Docket No. 47653-F(71789)
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	John C. Houck		
Serial Number:	09/189,130	Art Unit:	1631
Filed:	November 10, 1998	Examiner:	M. Borin
For:	SMALL PEPTIDES AND METHODS FOR TREATMENT OF ASTHMA AND INFLAMMATION		

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

CERTIFICATE OF MAILING

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November 6, 2001
Date

Judith A. Herrick
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BRIEF ON APPEAL

This is an appeal from the final rejection dated March 6, 2001 (Paper Number 19) wherein claims 1 and 4-8 are under examination and rejected. Three copies of this Brief are enclosed.

BRIEF ON APPEAL FEE

REAL PARTY IN INTEREST

The real party in interest is Histatek Inc., a Delaware corporation. The assignment of the inventors to this Histatek, LLC (the previous form of the corporation) was recorded at Reel/Frame 9001/0054.

RELATED APPEALS AND INTERFERENCES

An appeal has been filed in copending application Serial No. 09/190,043, which has related subject matter.

STATUS OF THE CLAIMS

Claims 1 and 4-8 stand finally rejected. Claims 9-23 are withdrawn from consideration due to a restriction requirement. Claims 1 and 4-8 are on appeal. A copy of the claims on appeal can be found in the attached Appendix.

STATUS OF THE AMENDMENTS

Claim 1 was amended in a communication filed April 5, 2000. No other amendments to the claims on appeal have been made. Amendments to the specification were made in a communication filed September 1, 1999 for purposes of identifying the SEQ I.D. Numbers to

comply with the Sequence disclosure as set forth in 37 CFR 1.821-1.825, in response to an Office Action dated June 24, 1999.

SUMMARY OF THE INVENTION

The invention is directed to a pharmaceutical composition having anti-inflammatory activity. The composition comprises a pharmacological carrier and an effective amount of a peptide having the formula f-Met-Leu-Phe-Phe (page 10, lines 13-21), to which reference is made also as "HK-X" (page 21, lines 9-10). The peptide is prepared by conventional small peptide chemistry techniques (page 11, lines 10-13). Methods of using pharmaceutical compositions, including doses, routes of administration, pharmaceutical carriers, etc., are described on page 11, line 15 through page 15, line 30. The claimed peptide is useful for treating inflammation associated with ailments such as asthma, arthritis, anaphylaxis, chronic obstruction pulmonary disease and chronic inflammatory bowel disease (page 10, lines 18-21).

The claimed peptide is effective in inhibiting inflammation. These anti-inflammatory properties include inhibition of mast cell degranulation (examples 2-12, line 28 through page 19, to line 27); and reduction of migration and aggregation of lymphocytes, eosinophils and neutrophils to a site of inflammation (page 25, line 7 through page 26, to line 18).

The examples describe a well-established mouse model for assessing the treatment effects of compounds on inhaled allergens. Allergic response is induced by treating mice with OVA, which manifests in mucous accumulation in the airways. It was found that the claimed

peptide inhibits mucous accumulation at least as effectively as a well-known pharmaceutical, Zileuton® (page 26, line 20 through page 28, to line 21).

ISSUES

1. Claim 1 is rejected under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103 (a) as obvious over Kermode (*Biochem J.*, 276:715-723 (1991)).

2. Claims 1, 4-8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kermode (*Biochem J.*, 276:715-723 (1991)), and further in view of Goodman and Gilman (*The Pharmacological Basis of Therapeutics*, Ninth edition, 1998, p. 4-9).

GROUPING OF CLAIMS

The claims are separate for the purpose of the present appeal. The claims do **not** stand or all together.

ARGUMENT

Summary Of The Argument

The cited art, as a whole, teach that f-methionyl peptides are inflammatory agents. Although Gleisner (1981) suggests that some f-methionyl peptides may inhibit degranulation of mast cells and could potentially be a useful addition to the antihistaminic drugs, the specific disclosure is limited to *in-vitro* testing of f-Met-Leu-Phe and later publications (of record)

including the publication by Kermode (1991), on which the examiner relies, teach that f-methionyl peptides are inflammatory agents.

Further, Kermode states that f-Met-Leu-Phe-Phe (herein sometimes called "HK-X") was the most potent of the seven formyl peptide analogs tested for stimulation of degranulation and chemotaxis including f-Met-Leu-Phe. Thus, there is no suggestion that f-Met-Leu-Phe-Phe has any useful therapeutic effect, much less an anti-imflammatory effect.

F-methionyl peptides have been used to study and understand the inflammatory response, such as caused by infection with bacteria. There has never been even a hint of a suggestion that a doctor should treat an infection with fMLP or any f-methionyl peptide. Indeed, prior to the present invention, those skilled in the art would have expected that such a treatment would aggravate the pro-inflammatory response already caused by the infection and create further damage to tissue (Declaration of Dr. Lipani, paragraph 9). No doctor would administer a pharmacological composition to induce a "pro-inflammatory" response (Declaration of Dr. Lipani, paragraph 11).

None of the cited art, nor any publications of which Applicant is aware, teach the use of the presently claimed f-Met-Leu-Phe-Phe as a pharmaceutical composition for any beneficial purpose. Much less is there any suggestion that f-Met-Leu-Phe-Phe has an anti-inflammatory effect or is useful for treating an allergic reaction.

Only the present Applicant has discovered and taught this use.

Thus, it is not seen how the present invention would have been obvious to one of ordinary skill in the art.

It is respectfully submitted that the examiner has not made out even a *prima facie* case of obviousness. The cited art, as a whole, teach away from the present invention. However, even if there were some suggestion for the present invention in the cited art, the surprising and unexpected results provided by the composition of the peptide f-Met-Leu-Phe-Phe could not have been reasonably predicted even by those skilled in the art, much less by one of ordinary skill in the art.

The examiner states that Kermode teaches that f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are functional equivalents. However, Kermode shows that different formyl Met peptides are **not** functional equivalents. Further, the tests conducted by Dr. Clagett and submitted by declaration (of record) show that the first compound (prior art) has no anti-inflammatory effect while the second (claimed) compound has substantial anti-inflammatory effect. Thus, the claimed compound, f-Met-Leu-Phe-Phe, is clearly not the functional equivalent of f-Met-Leu-Phe.

Claims 4-8

Regarding claims 4-8, there is no suggestion in any of the cited art that f-Met-Leu-Phe-Phe would be useful if administered orally (claim 4), by inhalation (claim 5), as an aerosol (claim

6), topically (claim 7) or as a tablet (claim 8). Thus, the selection of a carrier for each mode of administration is a separate and distinct basis for patentability.

The Cited Art

Kermode et al.

In 1991, Kermode et al. reported that various compositions of f-Met peptides are potent **stimualtors** of degranulation. Indeed, Kermode et al. reported that **both** f-Met-Leu-Phe (prior art) **and** f-Met-Leu-Phe-Phe (present invention) **are potent stimulators** of degranulation of neutrophils and are chemotactic.

Kermode et al. reported a study to determine the mechanism by which formyl peptides stimulate neutrophil degranulation and chemotaxis (page 715, column 2, lines 3-15):

> One proposal for the neutrophil is that the **high-affinity form of the receptor** may be responsible for activation of some biological functions, notably chemotaxis, with the **low-affinity form** responsible for other functions, e.g. degranulation. Similar proposals have been made to explain the differential activation of a range of biological responses in several other cell types and with several other receptor agonists. The only evidence to date to support this hypothesis for the neutrophil, however, is derived from studies of the influence of various perturbations of the cell on both the receptor-binding pattern and the biological responses for a single chemotactic formyl peptide, the prototypical compound N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMet-Leu-Phe). [Emphasis added].

Kermode tested several different formyl peptides, including f-Met-Leu-Phe, and categorized them into "most potent" and "less potent". Furthermore, Kermode concluded that the "most potent" peptides bind to the high affinity form of the receptor, and that the "less

potent" peptides bind to the low affinity form of the receptor. The "most potent" peptides according to Kermode are f-Met-Leu-Phe-Phe and f-Met-Leu-Phe-NHBzl. The "less potent" peptides are f-Met-Leu-Phe, f-Nle-Leu-Phe, f-Nva-Leu-Phe and f-Val-Leu-Phe. Thus, even amongst different compositions of formyl peptides, according to Kermode, there are differences in potencies and in their mechanism of action.

Indeed, for example, Kermode teaches that (page 716, right column):

> [t]he logical interpretation of these data is thus that the high-affinity sites are the receptors that **initiate degranulation**. [Emphasis added.]

Because Kermode also teaches that f-Met-Leu-Phe-Phe binds to the high affinity receptor, one skilled in the art would have been expected to conclude that f-Met-Leu-Phe-Phe **initiates degranulation** of the neutrophils and, thus, is harmful.

Kermode postulated that the high affinity site was responsible for activiating chemotaxis, which also is harmful. Thus, it is not seen how any teaching of Kermode would lead one of ordinary skill in the art to make a pharmaceutical composition using f-Met-Leu-Phe-Phe.

Goodman and Gilman

Goodman and Gilman discuss the potential pros and cons of various routes of drug administration. Goodman and Gilman do not discuss **specific routes** of administration for **specific drugs**. Rather, they give a broad overview of drug administration and emphasize that there are many variables that influence the absorption, bioavailability and distribution of drugs. (See Goodman and Gilman pp. 4-5, 9.) One of the main teacnings of the article is that **the drug**

itself is a major reason for choosing a **specific route** of administration and no mention is made for administration of anti-inflammatory compositions. Furthermore, the appropriate carrier again depends on the composition and the use of the drug. Thus; the combination of Kermode with Goodman and Gilman fails to teach or suggest the invention of claim 1, 4-8.

Claims 4-8

Nothing in Goodman and Gilman teaches or suggests specifically how to administor the presently claimed composition containing f-Met-Leu-Phe-Phe, nor is there any teaching or suggestion for selecting a specific carrier for the administration of f-Met-Leu-Phe-Phe. Thus, there is no teaching or suggestion by Goodman and Gilman for selecting a carrier specifically to administer f-Met-Leu-Phe-Phe orally (claim 4), by inhalation (claim 5), as an aerosol (claim 6), topically (claim 7) or as a tablet (claim 8). Thus, the selection of a carrier for each mode of administration is a separate and distinct basis for patentability. There is no teaching or suggestion in the cited art for specifically administering f-Met-Leu-Phe-Phe orally (claim 4), by inhalation (claim 5), as an aerosol (claim 6), topically (claim 7) or as a tablet (claim 8).

Anderson et al.

Anderson et al. (reference AC) is not presently being relied on by the examiner. However, it is considered that the teachings of Anderson et al. are important for illustrating the state of the art at the time of the present invention.

In 1992, Anderson et al. reported structure activity studies of f-methionyl peptides. First,

the types of disorders that may be associated with formyl peptides are listed and then a mechanism for the cause of such disorders is suggested (page 249, first column, lines 1-10; page 254, second column, lines 32-41):

> **There is now a substantial body of evidence implicating bacterial F-met peptides in intestinal inflammatory disorders.** They induce adhesion, chemotaxis, superoxide production, and lysosomal enzyme release in neutrophil leukocytes; **can induce experimental colitis** in mice, rats, and rabbits; **increase intestinal vascular and mucosal permeability**; stimulate intestinal leukotriene synthesis; and are **spasmogenic for gut smooth muscle.**
>
> * * *
>
> Using a radioimmune assay with a rabbit polyclonal antibody raised against FMLP, we have identified FMLP immunoreactivity in both rat and human bile. The most likely source of this reactivity is formyl oligopeptide produced by intestinal bacteria and reaching the liver in portal blood. **Since the liver excretes such peptides in a largely unaltered form, they presumably retain their potential to induce inflammatory responses should they cross the biliary epithelium.** [Emphasis added].

Anderson concludes that (page 255, column 1):

> The association between biliary tract disorders and inflammatory bowel disease has long been thought to be related to the presence of bacterial products in bile, **and low-molecular-weight formyl-peptides could be important in this respect.** [Emphasis added].

Thus, the Anderson reference also **teaches away** from using formyl peptides and their analogues as for therapy. The studies of Anderson also support the notion that formyl peptides and their analogues may **cause inflammatory disorders** and thus **would not be useful** as pharmaceutical compounds.

Ferry et al.

Ferry et al. (reference AM) also is not presently being relied on by the examiner. However, it is considered that the teachings of Ferry et al. also are important for illustrating the state of the art at the time of the present invention.

In 1989, Ferry et al. recognized f-Met peptides as pro-inflammatory peptides. In fact, Ferry taught that administration of low molecular weight formyl peptides is **pro**inflammatory and, by whatever route, could cause **unwanted reactions or disorders**. For example, Ferry states on page 64, second column under Discussion:

> There is an increasing body of evidence suggesting that low molecular weight **proinflammatory** N-f-met oligopeptides **could play a role in intestinal inflammatory disorders**. All species of intestinal bacteria so far investigated produced such peptides in vitro and bioactive peptides have been demonstrated in colonic fluid obtained by in vivo dialysis techniques.
>
> In experimental animals **both colonic infusions and rectal administration of N-formyl methionyl-leucyl-phenylalanine (N-f-met-leu-phe) resulted in experimental colitis**, although the concentrations used in these studies were in the millimole range, at least three orders of magnitude greater than those estimated by bioassay of intestinal contents.
>
> **Systemic infusion** of radiolabeled f-met peptides in rats showed that intact peptide was rapidly excreted in bile and an enterohepatic circulation of f-met peptide was subsequently demonstrated. **Experimental acetic acid-induced colitis was associated with an eightfold increase in biliary excreation of labeled peptide following its instillation into colon loops.** [Emphasis added].

Thus, Ferry concluded from their own experimental data that (page 61, first column, lines 19-28):

> in the ileum both enzymic degradation and restricted mucosal permeability contribute to the intestinal barrier to luminal bacterial formyl oligopeptides. In the colon, however, enzymic mechanisms are less active and restricted mucosal permeability is the major factor. **Abnormalities of the intestinal mucosal barrier to proinflammatory bacterial peptides could play a role in**

inflammatory disorders of the gut. [Empahsis added.]

Although their conclusion focuses on administration of formyl peptides to the **unhealthy** intestine, they also suggest problems even if administered to **healthy** individuals. Ferry admits that their failure to find increased absorption to the intestine under normal conditions cannot in any way be used even to assume, much less to predict with reasonable certainty, that these peptides will have no adverse effect when administered to healthy individuals (paragraph bridging pages 65-66):

> **Changes in vascular permeability and blood flow (without changes in mucosal permeability) have been reported with f-met-leu-phe in rat small intestine** by Granger et al. and these effects were apparently not found in animals rendered neutropenic, suggesting an effect of f-met-leu-phe on neutrophil leukocytes in the microcirculation of the gut. More recently, **the same group reported increased mucosal permeability in response to ileal perfusion with f-met-leu-phe** (10^{-6}M). This observation supports that of Magnussen et al. The effect appears to be confined to the terminal ileum and to be leukocyte-dependent. **We failed to find increased ^{51}Cr-EDTA absorption with either f-met-leu-tyr (10^{-4}M) or f-met-leu-phe (10^{-4}M) alone over a 1-h period. The short period of observation and the infusion into loops rather than perfusion design may account for this. Our studies were simply designed as controls for our experiments with different agents rather than to investigate the inflammatory response and permeability changes secondary to leukocyte accumulation. Trace amounts of intact formyl peptides do escape the enzyme and mucosal permeability barriers and trace amounts of intact peptide (picomoles) were recovered in bile in our control studies.** The biological significance of these amounts awaits further studies. [Emphasis added].

Ferry suggests that the trace amounts of formyl peptide in bile **may be** a symptom of potential adverse effects even under healthy conditions but has not investigated this issue. However, based on the wealth of information provided by others, it is submitted that one of

ordinary skill in the art would consider it quite likely that trace amounts of formyl peptide in bile is a symptom of potential adverse health effects.

Ferry and Anderson support Kermode in teaching that f-Met peptides cause harmful effects. In view of these teachings, why would one of ordinary skill in the art even consider the use of f-Met peptides for treatment of an allergy reaction.

Indeed, although there are extensive publications relating to f-Met peptides, to Applicant's knowledge, none of them suggest administering such peptides for any beneficial effect.

Applicants arguments are supported by two declarations of Dr. Clagett and the declaration of Dr. Lipani.

Detailed Discussion Of The Rejections

1. Claim 1 is rejected under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103 (a) as obvious over Kermode (*Biochem J.*, 276:715-723 (1991)).

2. Claims 1, 4-8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kermode (*Biochem J.*, 276:715-723 (1991)), and further in view of Goodman and Gilman (*The Pharmacological Basis of Therapeutics*, Ninth edition, 1998, p. 4-9).

Kermode fails to teach or suggest that a pharmaceutical composition comprising a pharmacological carrier and a peptide having the formula f-Met-Leu-Phe-Phe has **anti-inflammatory** activity.

Kermode taught that fMLP peptides are **proinflammatory** due to their ability to stimulate chemotaxis and mast cell degranulation (page 721, right column, lines 41-53).

> ***Binding of a formyl peptide agonist to the receptor causes its conversion to a high-affinity state and triggers an immediate signal for degranulation**; this biological response thus parallels high-affinity binding. When the agonist is a less potent formyl peptide (such as fMet-Leu-Phe), this activated state is maintained only for a short time; a rapid transition occurs to a lower-affinity state incapable of sustaining a chemotactic signal (Fig. 6a). This transition does not affect the degranulation signal, but restricts the longer-duration signal for the chemotactic response; migration is thus limited. **The most potent analogues (such as fMet-Leu-Phe-Phe), in contrast, stabilize the activated high-affinity state in some way, thereby providing a longer duration signal and greater migration.*** [Emphases added.]

Furthermore, Kermode taught that different f-methionyl peptides have widely differing affinities for the fMLP peptide receptor (page 718, left column, lines 5-9).

> The equilibrium dissociation constant (K_d) for high-affinity binding had a range of **1300-fold** between the least potent (fVal-Leu-Phe) and the most potent (fMet-Leu-Phe-Phe) of the seven formyl peptide analogues, whereas the K_d for the low-affinity binding varied **9700-fold** (Table 1).*** [Emphasis added.]

Finally, Kermode stated that the strength of the binding of the f-mehtionyl peptide to the receptor correlated to the biological potency (i.e. its ability **stimulate** mast cell degranulation and chemotaxis to the site of inflammation) of the peptide (abstract, page 715, lines 5-6):

> ***The relative potencies of the formyl peptide analogues for stimulation of degranulation correlated will with their relative potencies for high-affinity, but not low-affinity, [receptor] binding.***

Thus, from Kermode, one of ordinary skill in the art would have expected that f-methionyl peptides have a **proinflammatory** activity and that fMLPP (presently claimed invention) is particularly potent in this regard. Furthermore, it would have been expected that the different fMLP peptides have a wide range of affinities for the receptor and that this, in turn, means their biological potencies vary widely.

The examiner asserts that "the knowledge that formyl peptides stimulate various functions of neutrophils which constitute defense reaction to infectious microorganisms would be sufficient motivation to an artisan to apply such agent as a pharmaceutical under conditions when **therapeutic stimulation** of such defense reaction to infectious microorganisms is required." However, such formyl peptides are taught to be **proinflammatory**. Although inflammation initiates a defense reaction, stimulating inflammation *per se* is not desirable. The examiner fails to provide any reference teaching that stimulating an inflammatory cascade is a desirable therapeutic goal. To the contrary, see Declaration of Dr. of Dr. Lipani, paragraphs 11, 17 (no doctor would administer a pharmacological composition to induce a pro-inflammatory response; it is unacceptable to use an inflammation promoting agent(e.g., f-met-leu-phe) as a therapeutic agent).

The formyl peptides and their proinflammatory activity have been known for many years. However, none of the cited references teach or suggest using them for any therapeutic purpose. Indeed, until the teaching of the present application, there has been no suggestion for making a pharmaceutical composition containing any formyl peptides, much less the specific peptide claimed presently.

Certainly, Kermode does not teach or suggest to one of ordinary skill in the art that the pharmaceutical composition of the present would be useful for any therapeutic purpose, much less that such composition has an **anti-inflammatory** activity. Indeed, Kermode et al., teach that both f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are potent stimulators of degranulation of neutrophils and are chemotactic.

Examiner further stated that "[t]he rejection provides an example of colony stimulating factor which, similarly to f-met peptides, can be either pro- or anti-inflammatory. Lack of comment to this example is understood as a silent agreement with Examiner's analysis."

Comments to this statement were submitted by Applicant, e.g., in Dr. Lipani's Declaration of April 12, 2000, at page 4, paragraph No. 10. For clarification, the Examiner's statement will be addressed briefly. The is mistaken that the reference, Burak et al, 1998, Abstract, teaches pro-inflammatory properties of colony-stimulating factor. The reference reports about a patient showing necrosis and inflammation and treating that patient with prednisone (an anti-inflammatory agent), 5-aminosalicylate (an anti-inflammatory agent), and

granulocyte colony- stimulating factor **for** neutropenia. CSFs are known to stimulate specific lineages of white cells in the bone marrow deficient patient (Lipani Decl., paragraph 10). It is not seen how one of ordinary skill in the art would have concluded from this report that any formyl peptide, much less, f-Met-Leu-Phe-Phe, should be administered to a patient for therapeutic purposes.

Thus, Applicant respectfully submits that the cited prior art teaches away from the present invention.

Applicant has tested the effects on inflammation (i.e. allergic response) induced by prior art peptides, namely fMLP (f-Met-Leu-Phe) discussed in Kermode and other references, as compared to peptides of the present invention, namely fMLPP (f-Met-Leu-Phe-Phe; "HK-X"). The results of these experiments are presented in the Declaration (12/04/00) of Dr. Clagett (of record).

The Examiner stated that the Declaration of Dr. Clagett was "noticed," but alleges that:

> "[e]ven though the declaration shows the effect of fMLPP alone, it is not sufficient to overcome the rejection as the claims are drawn to a composition, not to a particular method of use, and the reference teaches composition which reads on the composition as claimed."

The Examiner's basis the rejection as follows:

> "As for the use of f-Met-Leu-Phe-Phe, it is noted that applicants contend that the peptide does not have pro-inflammatory effect by itself, which is different from the action of f-Met-Leu-Phe. However, Gleisner teaches that even the latter peptide f-Met-Leu-Phe (which as

> argued by applicant, is a pro-inflammatory agent) inhibits mast cell degranulation and histamine release. Examiner has no reason to expect that f-Met-Leu-Phe-Phe which is demonstrated in Kermode as one of the most effective formyl Met peptides will not have effect similar to f-Met-Leu-Phe."

The declaration by Dr. Clagett (12/04/00) of record presents tests illustrating the different effects of fMLP alone, and of HK-X (fMLPP) both alone and in conjunction with fMLP in the mouse model. The results of these experiments are surprising and unexpected in view of the prior art teachings for f-Met peptides.

Applicant compared the effects of injecting fMLP or fMLP + fMLPP (HK-X) into the dorsum of mice feet and observed the effects on the injected tissue over time. Applicant found that injection of fMLP alone caused a strong inflammatory effect including massive cellular infiltration to the site of injection whereas simultaneous injection with fMLPP (HK-X) blocked this inflammatory response (91% inhibition). See the Declaration (12/04/00) of Dr. Clagett, paragraphs 13-16.

Briefly, in the experiments, there was subcutaneously injected into the dorsum of mice feet 200 μg of **fMLP** alone; 200 μg of HK-X (fMLPP) alone; 200 μg of fMLP and 200 μg of HK-X together; and as a control the vehicle (4% DMSO in Tyrode's solution).

The results showed that fMLP alone induced a potent chemotactic response. However, by itself, HK-X (fMLPP) was **not** chemotactic and HK-X **inhibited** the chemotactic capacity of fMLP when HK-X (fMLPP) and fMLP were administered together. Therefore, HK-X (fMLPP)

mechanism of action functions at the **earliest** stage of inflammation by **inhibiting** the recruitment of inflammatory cells. A second important property of HK-X (fMLPP) is that it also **inhibits** the action of a potent chemotactic agent.

In short, fMLP exhibited a **pro**-inflammatory or allergy stimulating activity in accord with the teachings of the prior art. However, surprisingly and unexpectedly (in view of the prior art) the fMLPP (HK-X) of the present invention exhibited an **anti**-inflammatory activity that blocked the pro-inflammatory response induced by fMLP. See the Declaration (12/04/00) of Dr. Clagett, paragraphs 13-16. Thus, even though the Examiner contends that he has "**no reason to expect** that f-Met-Leu-Phe-Phe, which is demonstrated in Kermode as one of the most effective formyl Met peptides, will not have a similar effect to f-Met-Leu-Phe", the results shown in the Declaration of Dr. Clagett have the **unexpected** result of being **anti**-inflammatory. Thus, the present composition has shown results that even the **Examiner could not have expected**.

The Examiner further states that "where the claimed and prior art products are identical or substantially identical in composition, a *prima facie* case of either anticipation or obviousness has been established."

However, the prior art fails to anticipate or render obvious the pharmaceutical composition of the present invention. It is erroneous to conclude that "a *prima facie* case of either anticipation or obviousness has been established." For example, Table 1 on page 15 of the present specification, shows that the closely related peptides f-Met-Phe and Met-Phe had little

inhibitory effect on mast cell degranulation. It is **not** obvious from any cited art that structurally similar compounds will have the same effect or the same potency.

Further, Kermode, Ferry and Anderson, which discuss the presently claimed f-Met-Leu-Phe-Phe, taught that the peptide has pro-inflammatory activity and, thus, would stimulate (or aggravate) the response to an allergic reaction, not treat it.

There is no teaching in any of the cited art that the claimed f-Met-Leu-Phe-Phe has any anti-inflammatory effect. F-methionyl peptides, particulary f-Met-Leu-Phe, have been studied because it is considered that the peptide is secreted by bacteria that cause infections and that the peptide produces the inflammation response. Thus, one of ordinary skill in the art would have expected that the treatment with f-Met-Leu-Phe or similar f-methionyl peptides would produce the inflammatory response, and no such treatment would be administered by a medical doctor (Lipani declaration, paragraphs 11, 17).

In the test conducted by Dr. Clagett, f-Met-Leu-Phe was used to stimulate the inflammatory response. However, prior to the present invention, one also would have expected f-Met-Leu-Phe-Phe to stimulate the inflammatory response (as taught by Kermode and **admitted** by the **examiner**). Yet, the administration of f-Met-Leu-Phe-Phe by Dr. Clagett had the opposite effect from what would have been expected. Instead of further stimulating the inflammation response, the f-Met-Leu-Phe-Phe provided an anti-inflammatory response that inhibited the

effect of f-Met-Leu-Phe. That is, indeed, a surprising and unexpected result of f-Met-Leu-Phe-Phe, and contrary to the teachings of the prior art.

The present application surprisingly and unexpectedly teaches that f-Met-Leu-Phe-Phe has an inhibitory effect on **both** mast cells and neutrophils. Applicant has discovered that f-Met-Leu-Phe-Phe **inhibits** inflammation at the **earliest stages** by inhibiting the recruitment of inflammatory cells to the site of inflammation.

Kermode et al. teach that various f-Met peptides are potent stimulators of degranulation. Indeed, Kermode et al. teach that both f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are potent stimulators of degranulation of neutrophils are chemotactic. Such characteristics and pro-inflammatory activity would lead one skilled in the art away from the presently claimed f-Met-Leu-Phe-Phe composition, in contrast to the Examiner's statement that "where the claimed and prior art products are identical or substantially identical in composition, a *prima facie* case of either anticipation or obviousness has been established."

In addition, the properties of the claimed composition teach away from any "substantially identical compositions" having allegedly "inherently" similar properties. For example, Kermode makes **no** suggestion for using formyl peptides for any therapy. There is not even a hint of a suggestion by Kermode that such peptides will be useful for any therapeutic treatment.

Based on Kermode, one skilled in the art would be expected to conclude that f-Met-Leu-

Phe-Phe **initiates degranulation** of the neutrophils and thus is harmful. Kermode also postulated that the high affinity site was responsible for activating chemotaxis, which also is harmful. Thus, it is not seen how any teaching of Kermode would lead one of ordinary skill in the art to make a pharmaceutical composition as claimed herein. Indeed, the first discovery that the claimed f-Met peptides provide useful biological properties was made by Applicant. Indeed, this useful property has been found only in the few claimed peptides, not in all f-Met peptides.

The examiner cites Kermode, *Biochem. J.* (1991) **276**, as disclosing that formyl Met peptides compositions, such as f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are functional equivalents. However, the tests reported in the Declaration of Dr. Clagett establish clear and convincing evidence to the contrary. It is clear from the tests conducted by Dr. Clagett and submitted in the declaration that f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are **not** functional equivalents.

Further, it is not seen how the properties discovered by Applicant for f-Met-Leu-Phe-Phe would have been reasonably predictable from the published properties of f-Met-Leu-Phe, or from the prior art as a whole.

The present application surprisingly and unexpectedly teaches that f-Met-Leu-Phe-Phe has an inhibitory effect on **both** mast cells and neutrophils. Applicant has discovered that f-Met-Leu-Phe-Phe **inhibits** inflammation at the **earliest stages** by inhibiting the recruitment of inflammatory cells to the site of inflammation.

Applicant teaches that f-Met-Leu-Phe-Phe **inhibits** all of the above responses. Based on the properties of f-Met-Leu-Phe-Phe as described in the prior art, it would not have been obvious to anyone skilled in the art, much less one of ordinary skill in the art, to use f-Met-Leu-Phe-Phe for any treatment, much less for **downregulation** of the inflammatory response.

Prior to the present discovery by Applicant, no one would have considered that the properties of f-Met-Leu-Phe-Phe would be beneficial to treat an allergic reaction. See the Declaration of Dr. Lipani (12/04/00), paragraph 17. The surprisingly remarkable inhibitory activities of the peptides of the present invention would not have been obvious to one of ordinary skill in the art from the prior art teachings. See the Declaration of James Clagett, paragraphs 7-18.

The Examiner also has stated that:

> "the knowledge that formyl peptides stimulate various functions of neutrophils which constitute defense reaction to infectious microorganisms would be a sufficient motivation to an artisan to apply such agent as a pharmaceutical under conditions when therapeutic stimulation of such defense reaction to infectious microorganisms is required."

Once again, the Examiner has totally missed the point. The examiner is referring to pro-inflammatory responses. There is no evidence in the record of any instance where " therapeutic stimulation of such defense reaction to infectious microorganisms is required." Further, the claimed composition of the present invention, as shown by the data in the application (Table 1,

page 19 and figures 6) and Dr. Clagett's Declaration,(paragraphs 10, 12-18) inhibits the pro-inflammatory responses. The claimed composition, has anti-inflammatory responses, thus there would **not** be sufficient motivation to "**stimulate** various functions of neutrophils", (emphasis added). There has never been even a hint of a suggestion that a doctor should treat an infection with fMLP. Indeed, such a treatment would aggravate the pro-inflammatory response already caused by the infection and create further damage to tissue. (Declaration of Dr. Lipani, paragraph 9) No doctor would administer a pharmacological composition to induce a "pro-inflammatory" response. (Declaration of Dr. Lipani, paragraph 11)

Claims 4-8

The Examiner also objects to claims 4-8 based on Goodman and Gilman (Office Action dated 06/28/00, paper no. 14), that "routes of administration and appropriate carriers .... have been routinely determined."

Goodman and Gilman discuss the potential pros and cons of various routes of drug administration. Goodman and Gilman do not discuss **specific routes** of administration for **specific drugs**. Certainly, there is no teaching for how to administer f-Met-Leu-Phe-Phe. Rather, they give a broad overview of drug administration and emphasize that there are many variables that influence the absorption, bioavailability and distribution of drugs. (See Goodman and Gilman pp. 4-5, 9.) One of the main features of the article is that **the drug itself** is a major reason for choosing a **specific route** of administration and no mention is made for administration of anti-inflammatory compositions. Furthermore, the appropriate carrier again depends on the

composition of the drug. Thus, routes of administration, carriers cannot be universally applied to any drug. As Goodman and Gilman emphasize, the drug itself, is the determinative factor for choosing the best route and carrier for administration. These factors cannot be predicted by the Goodman reference. There is no teaching or suggestion in Goodman and Gilman to specifically select any particular carrier or specific method for administration of f-Met-Leu-Phe-Phe.

Accordingly, applicants respectfully submit that Kermode (*Biochem J.*, 276:715-723 (1991)) alone, or in view of Goodman and Gilman, does not teach or suggest the presently claimed invention to one of ordinary skill in the art.

Thus, given the many teachings that f-Met peptides are harmful and corresponding the lack of incentive to administer the f-Met peptides for therapeutic effect, one of ordinary skill in the art would not have been motivated to make and use pharmaceutical composition of the present invention.

In view of the above, it is not seen how the present invention would have been obvious to one of ordinary skill in the art.

A favorable decision reversing the rejections of the examiner is respectfully requested.

Respectfully submitted,

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APPENDIX

Claims on Appeal

1. A pharmaceutical composition having anti-inflammatory activity comprising a pharmacological carrier and an anti-inflammatory effective amount of a peptide having the formula f-Met-Leu-Phe-Phe.

4. The pharmaceutical composition of claim 1, wherein said carrier is selected for administration of the peptide orally.

5. The pharmaceutical composition of claim 1, wherein said carrier is selected for administration of the peptide by inhalation.

6. The pharmaceutical composition of claim 1, wherein said composition is an aerosol composition.

7. The pharmaceutical composition of claim 1, wherein said carrier is selected for administration of the peptide topically.

8. The pharmaceutical composition of claim 1, wherein said carrier is selected for administration of the peptide by tablet.